PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PCT-70014	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/EP2005/000840	International filing date *(day/month/year)* 28.01.2005	Priority date *(day/month/year)* 30.01.2004

International Patent Classification (IPC) or national classification and IPC
INV. C07D487/04 C07D417/12 C07D417/04 C07D277/34 A61K31/4188 A61K31/427

Applicant
CEPA SCHWARZ PHARMA S.L. et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 7 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30.11.2005	15.03.2006

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/000840

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1, 2, 4, 6-12, 14-46	as originally filed
3	filed with telefax on 30.11.2005
5, 13	filed with telefax on 02.03.2006

Claims, Numbers

1(part)	as originally filed
1(part), 2-19	filed with telefax on 30.11.2005
20, 21	filed with telefax on 02.03.2006

Claims, Pages

48a	filed with telefax on 02.03.2006

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-22
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-22
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1- Reference is made to the following documents:

d1: WO 99/29687 A (JANSSEN PHARMACEUTICA N.V; WIGERINCK, PIET, TOM, BERT, PAUL; VERSCHUER) 17 June 1999 (1999-06-17)
d2: WO 03/029250 A (BAYER AKTIENGESELLSCHAFT; SCHERLING, DIETRICH; KARL, WOLFGANG; SEIDEL,) 10 April 2003 (2003-04-10)
d3: EP-A-0 352 613 (BAYER AG) 31 January 1990 (1990-01-31)

2- Novelty
The compound 73 (page 28) of d1 has been excluded from the scope of the claims by means of a disclaimer.
Present compounds differ from the compounds of d2 and d3 at least on account of the diaza- or thiazadione ring.
Accordingly, the requirements of Art. 33.2 PCT are met.

3- Inventive step
3.1- The applicant has set himself the task of providing compounds which are capable to modulate the 5-HT_{1A} receptor.
Documents d2 and d2 relate to compounds having the same use of present compounds.
Considering the chemical structures of the compounds disclosed in these two documents, it is considered that d3 represents the closest state of the art.
The experimental data disclosed in present Tables 1 and 2, make it credible that substantially all the compounds of formula (I) can be used as 5-HT_{1A}.
Accordingly, the objective technical problem can be formulated as the provision of further 5-HT_{1A} ligands.

3.2- The solution of this problem, represented by present compounds of formula (I) is regarded as non-obviuos, since there is no suggestion in d1 or d2 for preparing compounds including the present diaza- or thiazadione ring.
Hence, the requirements of Art. 33.3 PCT are met.

Re Item VI

Certain documents cited

d4: WO 2004/014915 A (CEPA SCHWARZ PHARMA S.L; DEL RIO ZAMBRANA, JOAQUIN; FRECHILLA MANSO, D) 19 February 2004 (2004-02-19)

- 2-[4-[2-(Phenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole, (e)

For these compounds (a, b, c, d, e), an in vivo functional characterization test was performed by the quantification of the hypothermia associated to the stimulation of the receptor. Furthermore, the neuroprotective effect was evaluated by in vitro experimental models using primary cultures of rat hippocampus exposed to serum deprivation (compounds a, d, and e), to a toxic concentration of glutamate (compound a), or incubated in conditions of hypoxia and absence of glucose (compound a). On the other hand, the determination of the in vivo neuroprotective action is evaluated both in the transient global ischemia model in gerbils (compounds a and e) and in the permanent focal ischemia model in rats (compound a).

WO 99/29687 shows the compound 73 that is encompassed by the present formula I.

SUMMARY OF THE INVENTION

The present invention relates to a group of cycloalkanedione derivatives which are invariably substituted with a chroman-2-yl residue, a 2-quinolyl residue or an –O-phenyl residue.

In extensive studies the inventors have surprisingly identified a class of compounds with a high affinity for the 5-HT_{1A} receptor and remarkable neuroprotective properties.

The 5-HT_{1A} affinity has been demonstrated by in vitro radioligand displacement tests. Likewise, their affinity for the serotonergic 5-HT_{2A}, 5-HT_3, 5-HT_4 and 5-HT_7 receptors, 5-HT transporter, adrenergic α_1 and dopaminergic D_2 receptors have been characterized. The functional character (agonist/antagonist) of the new ligands was studied, determining the inhibition of the stimulating effect of forskolin on adenylate cyclase and studying, furthermore, in vivo, the 5-HT_{1A} agonist character of the new compounds by hypothermia analysis. In the same way, the compounds of the present invention have shown in vitro neuroprotective action on primary cultures of rat hippocampus, considering those models of neuronal death (deprivation of trophic factors and deprivation of oxygen and glucose) wherein the serotonergic 5-HT_{1A} agonists are more effective. The protective effect was also studied for cerebral infarction induced by permanent occlusion in the middle cerebral artery

dioxothiazolidine, 3-[6-[(chroman-2-yl)methylamino]hexyl]-2,4-dioxothiazolidine, 2-[4-[2-(phenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole or 3-[4-[2-(phenoxy)ethylamino]butyl]-2,4-dioxothiazolidine; (*)

In a preferred embodiment, R_3 is preferably selected from the group consisting of chroman-2-yl, 2-quinolyl and -O-phenyl, wherein the phenyl residue is optionally substituted by a group chosen from C_1-C_6-alkoxy, C_1-C_6-alkyl, or halogen.

The present invention comprises three main embodiments:

(1) m is 1 and R_3 is optionally substituted chroman-2-yl
(2) m is 2 and R_3 is optionally substituted O-phenyl
(3) m is 1 and R_3 is optionally substituted 2-quinolyl

According to a first preferred main embodiment of the present invention, m is 1 and R_3 is chroman-2-yl, the phenyl ring of which is unsubstituted or substituted by one or more groups chosen from C_1-C_6-alkoxy, C_1-C_6-alkyl, halogen, C_2-C_6-alkenyl, halo-(C_1-C_6)-alkyl, halo-(C_1-C_6)-alkoxy, phenyl, phenyl(C_1-C_6)-alkyl, phenoxy, C_1-C_6-alkylcarbonyl, phenylcarbonyl, phenyl(C_1-C_6)alkylcarbonyl, C_1-C_6-alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, C_1-C_6-alkylcarbonylamino, hydroxy, cyano, nitro, amino, N-(C_1-C_6)-alkylamino, N,N-(C_1-C_6)-dialkylamino, carboxy, sulfo, sulfamoyl, sulfonylamino, (C_1-C_6)alkylaminosulfonylor (C_1-C_6)alkylsulfonylamino; wherein each alkyl is optionally substituted with hydroxy or amino. R_3 is preferably unsubstituted chroman-2-yl.

Unless specifically mentioned otherwise the term "chroman-2-yl" refers to an unsubstituted chroman-2-yl residue.

According to a first embodiment of this first preferred main embodiment of the invention, R_1 and R_2 are methylene groups bound together forming with the heterocyclic ring a 5- or 6- membered ring and R_4 is N.

Those compounds wherein m is 1 and R_3 is chroman-2-yl, R_1 and R_2 are methylene groups bound together forming with the heterocyclic ring a 5- or 6-membered ring; R_4 is N; and X is selected from the group consisting of C_2-C_{10}-

(*) and is not 3-[3-[(chroman-2-yl)methylamino]propyl]-2,4-dioxoimidazolidine.

similarity with cerebral infarction than the cellular death caused by serum deprivation in the culture medium. Whilst in this last model, the death, of an apoptotic nature, takes place due to the elimination of the trophic factors from the medium, oxygen and glucose deprivation causes a death with similar characteristics to that which takes place in an ischemic stroke. In accordance with the predictive value of these in vitro studies, the compound (a) of PCT/ES03/00394 only exercises a protective effect against cerebral infarction induced by permanent occlusion of the middle cerebral artery in rats at a dose of 2 mg/kg. On the other hand, as is indicated further on in the present specification, compound (e) disclosed herein, with a neuroprotective effect equal to (-)-BAYx3702 and about four times greater than the compound (a) of the previous document against death due to anoxia, significantly reduces the volume of cortical infarction in the same focal ischemia model in the rat at a much lower accumulated dose, 0.04 mg/kg, similar to the effective dose of (-)-BAYx3702 in this model.

Taking into account its 5-HT_{1A} receptor affinity and its neuroprotective capacity, the compounds of formula (I) (*) are useful in the treatment and/or prevention of pathological states wherein the 5-HT_{1A} receptor modulators and particularly agonists are indicated, such as, for example, the treatment and/or prophylaxis of cerebral damage caused by thromboembolic stroke or traumatic brain damage, as well as the treatment and/or prevention of Parkinson's disease, depression including particularly endogenous "major" depression, migraine, pain, psychosis such as e.g. schizophrenia; mood disorders, such as anxiety disorders (e.g. obsessional compulsive disorders, generalised anxiety) and aggressive disorders (including mixed aggressive-anxiety/depressive disorders); urinary tract disorders, in particular urinary incontinence, e.g. stress incontinence.

Therefore, according to a second aspect of the present invention, it relates to a pharmaceutical composition that comprises a therapeutically effective quantity of any of the compounds of formula (I) together with a pharmaceutically acceptable carrier.

A third aspect of the present invention relates to the use of compounds of formula (I) (*) in the manufacture of a medicament for the treatment and/or prophylaxis of Parkinson's disease, of the cerebral damage caused by

(*) or 3-[3-[(chroman-2-yl)methylamino]propyl]-2,4-dioxoimidazolidine

dioxothiazolidine, 3-[6-[(chroman-2-yl)methylamino]hexyl]-2,4-dioxothiazolidine, 2-[4-[2-(phenoxy)ethylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]imidazole or 3-[4-[2-(phenoxy)ethylamino]butyl]-2,4-dioxothiazolidine; insert page 48a

2. Compound according to claim 1, wherein R_3 is selected from the group consisting of chroman-2-yl, 2-quinolyl and -O-phenyl, wherein the phenyl residue is optionally substituted by a group chosen from C_1-C_6-alkoxy, C_1-C_6-alkyl, or halogen;

3. Compound according to claim 1 or 2, wherein m is 1 and R_3 is chroman-2-yl.

4. Compound according to claim 3, wherein R_1 and R_2 are methylene groups bound together forming with the heterocyclic ring a 5- or 6- membered ring; and R_4 is N.

5. Compound according to any of claims 3 to 4, wherein X is selected from the group consisting of C_2-C_{10}-alkyl, (*E*)-2-butenyl, 3-methylbenzyl or 4-methylbenzyl.

6. Compound according to claim 3, wherein R_1 is H, R_2 is absent and R_4 is S.

7. Compound according to claim 6, wherein n is 0 and X is C_2-C_{10}-alkyl.

8. Compound according to claim 1 or 2, wherein m=2 and R_3 is –O-phenyl, wherein the phenyl residue is optionally substituted by one or more groups chosen from C_1-C_6-alkoxy, C_1-C_6-alkyl, halogen, C_2-C_6-alkenyl, halo-(C_1-C_6)-alkyl, halo-(C_1-C_6)-alkoxy, phenyl, phenyl(C_1-C_6)-alkyl, phenoxy, C_1-C_6-alkylcarbonyl, phenylcarbonyl, phenyl(C_1-C_6)alkylcarbonyl, C_1-C_6-alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, C_1-C_6-alkylcarbonylamino, hydroxy, cyano, nitro, amino, N-(C_1-C_6)-alkylamino, N,N-(C_1-C_6)-dialkylamino, carboxy, sulfo, sulfamoyl, sulfonylamino, (C_1-C_6)alkylaminosulfonyl or (C_1-C_6)alkylsulfonylamino; or wherein the phenyl ring is substituted by two neighbouring residues, which together with the phenyl ring to which they are attached form tetrahydronaphthyl.

9. Compound according to claim 8, wherein the phenyl group is optionally substituted by one or more groups chosen from phenyl, C_1-C_6-alkoxycarbonyl,

and is not 3-[3-[(chroman-2-yl)methylamino]-2,4-dioxoimidazoidine.

C_1-C_6-alkylcarbonylamino, C_1-C_6-alkoxy, C_1-C_6-alkyl, halo-(C_1-C_6)-alkyl, or halogen or wherein the phenyl group is substituted by two neigbouring residues, which together with the phenyl group to which they are attached form tetrahydronaphthyl.

10. Compound according to claim 9, wherein the phenyl residue is optionally substituted by one or more groups chosen from methoxy, ethoxy, propoxy, isopropoxy, ethyl, propyl, isopropyl, bromide, trifluoromethyl, methylamide or ethoxycarbonyl.

11. Compound according to any of claims 8 to 10, wherein the phenyl group is substituted in *ortho*- and/or *meta*- position.

12. Compound according to any of claims 8 to 11, wherein R_1 and R_2 are methylene groups bound together forming with the heterocyclic ring a 5- or 6-membered ring; and R_4 is N.

13. Compound according to any of claims 8 to 12, wherein n is 0 and X is C_2-C_{10}-alkyl.

14. Compound according to any of claims 8 to 11, wherein R_1 is H and R_2 is absent and R_4 is S.

15. Compound according to claim 14, wherein n is 0 and X is C_2-C_{10}-alkyl.

16. Compound according to claims 1 or 2, wherein m is 1 and R_3 is 2-quinolyl.

17. Compound according to claim 16, wherein R_1 and R_2 are methylene groups bound together forming with the heterocyclic ring a 5- or 6- membered ring; R_4 is N.

18. Compound according to any of claims ~~X~~ 16 to ~~X~~ 17, wherein n is 0; and X is C_2-C_{10}-alkyl.

19. Compound according to claim 1, wherein the compound is selected from:

(a) 2-[4-[(Chroman-2(*R*)-yl)methylamino]butyl]-1,3-dioxoperhydropyrrolo[1,2-

20. Pharmaceutical composition which comprises a therapeutically effective amount of a compound as claimed in any of claims 1 to 19 and, pharmaceutically acceptable carriers.

~~21. Use of a compound of any of claims 1 to 19 or 3-[3-[(chroman-2-yl)methylamino]-2,4-dioxoimidazolidine for the preparation of a medicament for the treatment and/or prophylasis of pathological states in which 5-HT1A agonists are indicated.~~

~~22. The use according to claim 21 in the preparation of a medicament for the treatment and/or prophylasis of Parkinson Disease, cerebral damage by thromboembolic ictus, craneoencephalic traumatisms, depression, migraine, pain, psychosis, anxiety disorders, aggressive disorders or urinary tract disorders.~~

21. Use of a compound of formula I according to any of claims 1 to 19, wherein the disclaimer to 3-[3-[(chroman-2-yl)methylamino]propyl]-2,4-dioxoimidazolidine does not apply, for the preparation of a medicament for the treatment and/or prophylaxis of Parkinson Disease, cerebral damage by thromboembolic ictus, craneoencephalic traumatisms, depression, migraine, pain, psychosis, anxiety disorders, aggressive disorders or urinary tract disorders.